Spray Dried Lactose Monohydrate, NF, Ph. Eur., JP, BP
(Note: Identical to FMC Corporation's SuperTab Lactose product.)

Description of Lactose Powder:

This lactose powder is specifically engineered for pharmaceutical direct compression tableting and is particularly well-suited in high dose formulations of poorly compressible actives. It is a free-flowing, white, spray-dried powder consisting of spherical particles. Each sphere is composed of minute lactose alpha-monohydrate crystals bonded with amorphous lactose. Additionally, the feedstock of this lactose powder is sourced from one of the world's uniquely pollution-free rural environments, and is remarkably pure even before processing.

Benefits:

- Excellent flow characteristics
- Improved tablet weight uniformity
- Exceptional carrying capacity
- Rapid tablet disintegration
- Excellent compressibility
- Low hygroscopicity
- Low reactivity with active ingredients
- Excellent physical, chemical and microbiological stability
- Solubility aids in drug dissolution

Note: This lactose powder is manufactured in New Zealand by The Lactose Company of New Zealand, Ltd.

Regulatory Status of this Lactose Powder:

This spray -dried lactose monohydrate meets the standards set forth in the United States Parmacopeia/National Formulary, European Pharmacopoeia, Japanese Pharmacopoeia and the Food Chemicals Codex. It is manufactured in accordance with current Good Manufacturing Practice, and is in compliance with the Federal Food, Drug and Cosmetic Act, as amended, and applicable regulations.

An experimental evaluation of powder rheology

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Powders are used extensively in the pharmaceutical industry and yet they are inherently difficult to characterise with regards their flowability. Powder flow properties are critical in the development and processing of solid dosage forms. Traditional flow measurement includes evaluation of the packing properties of the material by bulk density measurements such as Carr's compressibility index, Carr (1965), or determination of the critical orifice diameter. The aim of this investigation was to evaluate two newer techniques for determining flow, the Aeroflow (Amherst Process Instruments) which evaluates dynamic powder flow characteristics based on deterministic chaos theory, and the FT3 Powder Rheometer (Freeman Technology) which measures the forces causing deformation of a powder bed as a blade is forced through a column of powder at a required flow rate and pattern. In addition, the operating parameters and limitations of the instruments in comparing flow properties of materials of different particle size distributions and with the addition of different amounts of lubricant were established. The materials used were lactose DMV 110M and spray dried lactose DCL 11 (both Pharmatose), sieved size fractions of DVM 110M (45-75μm and 106-180μm) and magnesium stearate (Mg St) employed at either 0.5% or 1.0%w/w level blended with 45-75μm size fraction for 5 mins using a Turbula mixer. Carr's compressibility indices (CC, %) and Hausner ratios (HR) were determined for the materials. The Aeroflow drum was rotated at 60s per revolution for 300s. Results from the Aeroflow are expressed as mean time to avalanche (MTA, a measure of flowability) and the scatter (S, defines the regularity of the flow behaviour). The forces acting on the blade of the FT3 are converted to energy and are the basis of the flowability measurements and indices quoted are Basic Flowability (BF, the energy required to establish flow) and the Flow Rate Flowability Index (FRFI, the ratio of energy consumed at low and high tip speed). Results determined but not shown in Table 1 include hysteresis and compaction indices. Bulk density measurements showed differences in flow between different size fractions and between crystalline and spray dried material but no differences in flow indices with the addition of Mg St.

Table 1: Powder flow data for lactose, mean of 3 (SD)

sample	BF (mJ)	FRFI	MTA (s)	S	CC %	HR
DVM 110M	467 (19)	1.25 (0.08)	2.16 (0.10)	1.07 (0.07)	12.99	1.14
DCL 11	434 (18)	1.12 (0.03)	2.23 (0.09)	0.89 (0.09)	9.93	1.11
106-180μm	466 (52)	1.19 (0.01)	1.50 (0.07)	0.82 (0.82)	7.55	1.09
45-75μm	272 (4)	2.14 (0.02)	3.40 (0.08)	1.12 (0.18)	23.66	1.31
45-75μm +0.5%MgSt	142 (21)	1.61 (0.27)	3.39 (0.08)	1.05 (0.07)	-	-
45-75μm +1.0% MgSt	145 (11)	1.88 (0.12)	3.06 (0.26)	1.02 (0.04)	25.48	1.34

There were no significant differences in MTA and S values for DVM110M and DCL11, or with the addition of Mg St to the 45-75μm material, but the Aeroflow showed particle size related differences in flow behaviour. The avalanching method showed the 106-180μm material to exhibit the best flow properties with MTA closest to zero and low scatter value. The FT3 detected differences with respect to particle size and morphology. Addition of Mg St reduced energy required to establish flow and lowered the FRFI but no significant differences were found between using 0.5 or 1.0%w/w MgSt. An optimum MgSt content to achieve a FRFI of unity of an 'ideal' powder has yet to be determined. The BF value which is dependent on prevailing conditions, should be reported in conjunction with FRFI and compaction index when assessing flowability.

Carr, R. L. (1965) Chem. Eng. 72: 163-168

...ministration:
...myelet support.
...outlet port at bottom of container.
...set. Refer to complete directions
...

...AND STABILITY
...constituted as directed with sterile
...suspensions of ZINACEF for IM injec-
...satisfactory potency for 24 hours at room tem-
...hours under refrigeration (5°C).
...mentioned above any unused suspensions
...discarded.
...When the 750-mg, 1.5-g, and 7.5-g pharmacy
...constituted as directed with sterile water for
...ZINACEF solutions for IV administration
...satisfactory potency for 24 hours at room tempera-
...hours (750-mg and 1.5-g vials) or for 7 days
...bulk vial) under refrigeration (5°C). More
...such as 750 mg or 1.5 g plus 100 mL of sterile
...5% dextrose injection, or 0.9% sodium
...also maintain satisfactory potency for 24
...temperature and for 7 days under refrigera-
...
...may be further diluted to concentrations of
...and 60 mg/mL in the following solutions and will
...at least 10% activity for 24 hours at room temper-
...at least 7 days under refrigeration: 0.9% sodium
...injection; 1/6 M sodium lactate injection; ringer's
...injection, USP; lactated ringer's injection, USP; 5% dex-
...0.2% sodium chloride injection; 5% dextrose injec-
...dextrose and 0.45% sodium chloride injection; 5%
...dextrose and 0.225% sodium chloride injection; 10% dex-
...injection; and 10% invert sugar in water for injection.
...solutions should be discarded after the time periods
...noted above.
...ZINACEF has also been found compatible for 24 hours at
...room temperature when admixed in IV infusion with hepa-
...rin (10 and 50 U/mL) in 0.9% sodium chloride injection and
...sodium chloride (10 and 40 mEq/L) in 0.9% sodium chlo-
...ride injection. Sodium bicarbonate injection, USP is not
...recommended for the dilution of ZINACEF.
...750-mg and 1.5-g ZINACEF ADD-Vantage vials, when
...diluted in 50 or 100 mL of 5% dextrose injection, 0.9% so-
...dium chloride injection, or 0.45% sodium chloride injection,
...may be stored for up to 24 hours at room temperature or for 7
...days under refrigeration.
...**Stability:** Constitute the 750-mg, 1.5-g, or 7.5-g vial
...as directed for IV administration in Table 2. Immediately
...withdraw the total contents of the 750-mg or 1.5-g vial or 8
...mL from the 7.5-g bulk vial and add to a Baxter
...VIAFLEX® MINI-BAG™ containing 50 or 100 mL of 0.9%
...sodium chloride injection or 5% dextrose injection and
...mix well. Frozen solutions are stable for 6 months when stored
...at -20°C. Frozen solutions should be thawed at room tem-
...perature and not refrozen. Do not force thaw by immersion
...in water baths or by microwave irradiation. Thawed solu-
...tions may be stored for up to 24 hours at room temperature
...or 7 days in a refrigerator.
...Parenteral drug products should be inspected visu-
...ally for particulate matter and discoloration before adminis-
...tration, whenever solution and container permit.
...Other cephalosporins, ZINACEF powder as well as
...solutions and suspensions tend to darken, depending on stor-
...age conditions, without adversely affecting product potency.
...**Directions for Dispensing: *Pharmacy Bulk Package —Not
...for Direct Infusion:*** The pharmacy bulk package is for use
...in a pharmacy admixture service only under a laminar flow
...hood. Entry into the vial must be made with a sterile trans-
...fer set or other sterile dispensing device, and the contents
...withdrawn in aliquots using aseptic technique. The use of
...a syringe and needle is not recommended as it may cause leak-
...age. (SEE DOSAGE AND ADMINISTRATION). AFTER INI-
...TIAL WITHDRAWAL USE ENTIRE CONTENTS OF VIAL
...PROMPTLY. ANY UNUSED PORTION MUST BE DIS-
...CARDED WITHIN 24 HOURS.

...SUPPLIED
...ZINACEF in the dry state should be stored between 15° and
...30°C (59° and 86°F) and protected from light. ZINACEF is a
...white to off-white powder supplied in vials and infusion
...containers as follows:
...NDC 0173-0352-31 750-mg* Vial (Tray of 25)
...NDC 0173-0354-35 1.5-g* Vial (Tray of 25)
...NDC 0173-0353-32 750-mg* Infusion Pack (Tray of 10)
...NDC 0173-0356-32 1.5-g* Infusion Pack (Tray of 10)
...NDC 0173-0400-00 7.5-g* Pharmacy Bulk Package (Tray of 6)
...NDC 0173-0436-00 750-mg ADD-Vantage® Vial (Tray of 25)
...NDC 0173-0437-00 1.5-g ADD-Vantage® Vial (Tray of 10)
...*The ADD-Vantage vials are to be used only with Ab-
...bott ADD-Vantage diluent containers).
...Stable frozen as a premixed solution of cefuroxime so-
...dium should not be stored above −20° C. ZINACEF is sup-
...plied in 50-mL, single-dose, plastic containers as fol-
NDC 0173-0424-00 750-mg* Plastic Container (Carton of 24)
NDC 0173-0425-00 1.5-g* Plastic Container (Carton of 24)
*Equivalent to cefuroxime.

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Susceptibility Testing.* Third Informational Supplement. NCCLS Document M100-S3, Vol. 11, No. 17. Villanova, Pa: NCCLS; 1991.
2. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31-41.

February 1996/RL-229

Shown in Product Identification Guide, page 315

ZOVIRAX® Capsules B
ZOVIRAX® Tablets B
ZOVIRAX® Suspension B
[zō″vī′răx]
(acyclovir)

DESCRIPTION

ZOVIRAX is the brand name for acyclovir, an antiviral drug. ZOVIRAX Capsules, Tablets, and Suspension are formulations for oral administration. Each capsule of ZOVIRAX contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose, magnesium stearate, and sodium lauryl sulfate. The capsule shell consists of gelatin, FD&C Blue No. 2, and titanium dioxide. May contain one or more parabens. Printed with edible black ink.

Each 800 mg tablet of ZOVIRAX contains 800 mg of acyclovir and the inactive ingredients FD&C Blue No. 2, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Each 400 mg tablet of ZOVIRAX contains 400 mg of acyclovir and the inactive ingredients magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Each teaspoonful (5 mL) of ZOVIRAX Suspension contains 200 mg of acyclovir and the inactive ingredients methylparaben 0.1% and propylparaben 0.02% (added as preservatives), carboxymethylcellulose sodium, flavor, glycerin, microcrystalline cellulose, and sorbitol.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one.

Acyclovir is a white, crystalline powder with a molecular weight of 225 daltons, and a maximum solubility in water of 2.5 mg/mL at 37°C.

CLINICAL PHARMACOLOGY

Mechanism of Antiviral Effects: Acyclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against human herpes viruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). In cell culture, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV, and CMV.[1]

The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV, and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV, and EBV[2] converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.[3] Acyclovir triphosphate interferes with herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular α-DNA polymerase, but to a lesser degree. In vitro, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-DNA polymerase.[4] When incorporation occurs, the DNA chain is terminated.[5,6] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic in vitro for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase is less sensitive to the effects of the active form. The mode of acyclovir phosphorylation in cytomegalovirus-infected cells is not clearly established, but may involve virally induced cell kinases or an unidentified viral enzyme. Acyclovir is not efficiently activated in cytomegalovirus-infected cells, which may account for the reduced susceptibility of cytomegalovirus to acyclovir in vitro.

Microbiology: The quantitative relationship between the in vitro susceptibility of herpes simplex and varicella-zoster viruses to acyclovir and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (ID_{50}), vary greatly depending upon the particular assay used,[7] the cell type employed,[8] and the laboratory performing the test.[1] The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 μg/mL (plaque reduction in Vero cells) to 5.9 to 13.5 μg/mL (plaque reduction in green monkey kidney [GMK] cells).[1] The ID_{50} against HSV-2 ranges from 0.01 μg/mL to 9.9 μg/mL (plaque reduction in Vero and GMK cells, respectively).[1] Using a dye-uptake method in Vero cells,[9] which gives ID_{50} values approximately 5- to 10-fold higher than plaque reduction assays, 1417 HSV isolates (553 HSV-1 and 864 HSV-2) from approximately 500 patients were examined over a 5-year period.[10] These assays found that 90% of HSV-1 isolates were sensitive to ≤ 0.9 μg/mL acyclovir and 50% of all isolates were sensitive to ≤ 0.2 μg/mL acyclovir. For HSV-2 isolates, 90% were sensitive to ≤ 2.2 μg/mL and 50% of all isolates were sensitive to ≤ 0.7 μg/mL of acyclovir. Isolates with significantly diminished sensitivity were found in 44 patients. It must be emphasized that neither the patients nor the isolates were randomly selected and, therefore, do not represent the general population.

Most of the less sensitive HSV clinical isolates have been relatively deficient in the viral TK.[11-19] Strains with alterations in viral TK[20] or viral DNA polymerase[21] have also been reported. Prolonged exposure to low concentrations (0.1 μg/mL) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir-resistant strains.[22]

The ID_{50} against VZV ranges from 0.17 to 1.53 μg/mL (yield reduction, human foreskin fibroblasts) to 1.85 to 3.98 μg/mL (foci reduction, human embryo fibroblasts [HEF]). Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells or P3HR-1 lymphoblastoid cells by 1.5 μg/mL acyclovir. CMV is relatively resistant to acyclovir with ID_{50} values ranging from 2.3 to 17.6 μg/mL (plaque reduction, HEF cells) to 1.82 to 56.8 μg/mL (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.[1]

Pharmacokinetics: The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients. In one uncontrolled study of 35 immunocompromised patients with herpes simplex or varicella-zoster infection, ZOVIRAX Capsules were administered in doses of 200 to 1000 mg every 4 hours, 6 times daily for 5 days, and steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the final 200 mg dose were 0.49 μg/mL (0.47 to 0.54 μg/mL) and 0.31 μg/mL (0.18 to 0.41 μg/mL), respectively, and following the final 800 mg dose were 2.8 μg/mL (2.3 to 3.1 μg/mL) and 1.8 μg/mL (1.3 to 2.5 μg/mL), respectively. In another uncontrolled study of 20 younger immunocompetent patients with recurrent genital herpes simplex infections, ZOVIRAX Capsules were administered in doses of 800 mg every 6 hours, 4 times daily for 5 days; the mean steady-state peak and trough concentrations were 1.4 μg/mL (0.66 to 1.8 μg/mL) and 0.55 μg/mL (0.14 to 1.1 μg/mL), respectively.

In general, the pharmacokinetics of acyclovir in children is similar to adults. Mean half-life after oral doses of 300 mg/m² and 600 mg/m², in children ages 7 months to 7 years, was 2.6 hours (range 1.59 to 3.74 hours).

A single oral dose bioavailability study in 23 normal volunteers showed that ZOVIRAX Capsules 200 mg are bioequivalent to 200 mg acyclovir in aqueous solution; and in a separate study in 20 volunteers, it was shown that ZOVIRAX Suspension is bioequivalent to ZOVIRAX Capsules. In a different single-dose bioavailability/bioequivalence study in 24 volunteers, one ZOVIRAX 800 mg Tablet was demonstrated to be bioequivalent to four ZOVIRAX 200 mg Capsules.

In a multiple-dose crossover study where 23 volunteers received ZOVIRAX as one 200 mg capsule, one 400 mg tablet, and one 800 mg tablet 6 times daily, absorption decreased with increasing dose and the estimated bioavailabilities of acyclovir were 20%, 15%, and 10%, respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not dose proportional over the dosing range 200 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir were 0.83 and 0.46 μg/mL, 1.21 and 0.63 μg/mL, and 1.61 and 0.83 μg/mL for the 200, 400, and 800 mg dosage regimens, respectively.

In another study in 6 volunteers, the influence of food on the absorption of acyclovir was not apparent.

Following oral administration, the mean plasma half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. The mean renal excretion of unchanged drug accounts for 14.4% (8.6% to 19.8%) of the orally administered dose. The only urinary metabolite (iden-

Continued on next page